MAPT gene

microtubule associated protein tau

Normal Function

The *MAPT* gene provides instructions for making a protein called tau. This protein is found throughout the nervous system, including in nerve cells (neurons) in the brain. It is involved in assembling and stabilizing microtubules, which are rigid, hollow fibers that make up the cell's structural framework (the cytoskeleton). Microtubules help cells maintain their shape, assist in the process of cell division, and are essential for the transport of materials within cells.

Six different versions (isoforms) of the tau protein are produced in the adult brain. The isoforms vary in length from 352 to 441 protein building blocks (amino acids). A region of the protein called the microtubule-binding domain, which is the part of the protein that attaches (binds) to microtubules, also varies among the isoforms. In three of the isoforms, the microtubule-binding domain contains three repeated segments. In the other three isoforms, this domain contains four repeated segments. Typically, the brain has approximately the same amount of three-repeat isoforms and four-repeat isoforms. This balance appears to be essential for the normal function of neurons.

Health Conditions Related to Genetic Changes

frontotemporal dementia with parkinsonism-17

More than 40 mutations in the *MAPT* gene have been found to cause frontotemporal dementia with parkinsonism-17 (FTDP-17). Some of these mutations change single amino acids in the tau protein, most often in the microtubule-binding region. These mutations reduce tau's ability to bind to microtubules, which disrupts many important cell functions.

Other *MAPT* gene mutations change the way the gene's instructions are used to build the tau protein. Most of these mutations increase the production of tau with four repeated segments compared to the production of tau with three repeated segments. The resulting imbalance of tau isoforms in the brain interferes with the normal functions of brain cells.

In ways that are not fully understood, the *MAPT* gene mutations responsible for FTDP-17 lead to an accumulation of abnormal tau in neurons and other brain cells. These clumps of defective tau build up over time, although it is unclear what effect they have on cell function and survival. FTDP-17 is characterized by the gradual death of cells in areas of the brain called the frontal and temporal lobes. The frontal lobes are involved in reasoning, planning, judgment, and problem-solving, while the

temporal lobes help process hearing, speech, memory, and emotion. The loss of cells in these brain regions leads to the major features of FTDP-17, including changes in personality and behavior, speech and language abnormalities, and problems with movement.

progressive supranuclear palsy

Several mutations in the *MAPT* gene have been found to cause progressive supranuclear palsy. However, mutations in this gene appear to be a rare cause of this disorder.

At least one normal variation (polymorphism) in the *MAPT* gene has been associated with an increased risk of developing progressive supranuclear palsy. This polymorphism, known as the H1 haplotype, is found much more frequently in people with progressive supranuclear palsy than in the general population. It is unclear exactly how this genetic variation increases the risk of developing this disease.

The features of progressive supranuclear palsy appear to be related to abnormalities in the tau protein. In people with *MAPT* gene mutations, genetic changes disrupt the protein's normal structure and function. However, abnormal tau is also found in people without *MAPT* gene mutations. The defective tau protein assembles into abnormal clumps within neurons and other brain cells, although it is unclear what effect these clumps have on cell function and survival. Progressive supranuclear palsy is characterized by the gradual death of brain cells, particularly in structures deep within the brain that are essential for coordinating movement. This loss of brain cells underlies the major features of progressive supranuclear palsy, including problems with movement, vision, speech, and thinking (cognition).

other disorders

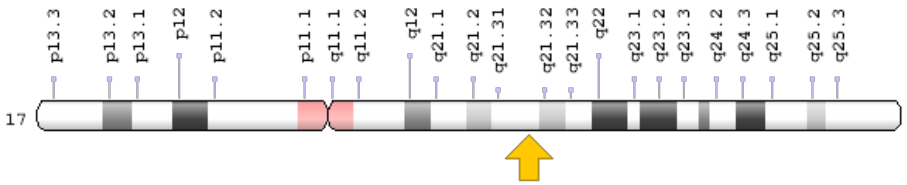
Mutations in the *MAPT* gene have also been found to cause other brain disorders similar to FTDP-17 and progressive supranuclear palsy. These disorders include corticobasal degeneration, tauopathy with respiratory failure, and a form of dementia with seizures (epilepsy). Although these conditions have somewhat different patterns of signs and symptoms, they all involve changes in personality, behavior, or cognition and problems with movement. The *MAPT* gene mutations responsible for these disorders lead to a buildup of abnormal tau in brain cells. Although the effect of tau accumulation on cell function and survival is unknown, these disorders are characterized by the death of brain cells in regions of the brain essential for cognition, emotion, and coordinating movement.

Because all of these diseases are characterized by an abnormal buildup of tau in the brain, they are known as tauopathies. Some researchers suggest that, instead of being described as separate disorders, the group of tauopathies caused by mutations in the *MAPT* gene should be considered as part of a spectrum with varying signs and symptoms.

Chromosomal Location

Cytogenetic Location: 17q21.31, which is the long (q) arm of chromosome 17 at position 21.31

Molecular Location: base pairs 45,894,382 to 46,028,334 on chromosome 17 (Homo sapiens Annotation Release 108, GRCh38.p7) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- DDPAC
- FLJ31424
- FTDP-17
- G protein beta1/gamma2 subunit-interacting factor 1
- MAPTL
- MGC138549
- microtubule-associated protein tau
- MSTD
- MTBT1
- MTBT2
- neurofibrillary tangle protein
- paired helical filament-tau
- PHF-tau
- PPND
- PPP1R103
- TAU
- TAU_HUMAN

Additional Information & Resources

Educational Resources

- Basic Neurochemistry (sixth edition, 1999): Microtubules Act as Both Dynamic Structural Elements and Tracks for Organelle Traffic
  https://www.ncbi.nlm.nih.gov/books/NBK28122/#A572
- The Cell: A Molecular Approach (second edition, 2000): Microtubules
  https://www.ncbi.nlm.nih.gov/books/NBK9932/

GeneReviews

- MAPT-Related Disorders
  https://www.ncbi.nlm.nih.gov/books/NBK1505

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28MAPT%5BTI%5D%29+OR+%28microtubule-associated+protein+tau%5BTI%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1800+days%22%5Bdp%5D

OMIM

- FRONTOTEMPORAL DEMENTIA
  http://omim.org/entry/600274
- MICROTUBULE-ASSOCIATED PROTEIN TAU
  http://omim.org/entry/157140

Research Resources

- Alzheimer Disease & Frontotemporal Dementia Mutation Database
  http://www.molgen.ua.ac.be/FTDmutations/Default.cfm?MT=1&ML=0&Page=Contexts&ID=4
- Atlas of Genetics and Cytogenetics in Oncology and Haematology
  http://atlasgeneticsoncology.org/Genes/GC_MAPT.html
- ClinVar
  https://www.ncbi.nlm.nih.gov/clinvar?term=MAPT%5Bgene%5D
- HGNC Gene Family: Protein phosphatase 1 regulatory subunits
  http://www.genenames.org/cgi-bin/genefamilies/set/694
- HGNC Gene Symbol Report
  http://www.genenames.org/cgi-bin/gene_symbol_report?q=data/hgnc_data.php&hgnc_id=6893

- NCBI Gene
  https://www.ncbi.nlm.nih.gov/gene/4137
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Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/gene/MAPT

Reviewed: March 2011
Published: March 21, 2017

Lister Hill National Center for Biomedical Communications
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